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Repeated seasonal influenza vaccination among elderly in Europe: Effects on laboratory confirmed hospitalised influenza

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ABSTRACT

In Europe, annual influenza vaccination is recommended to elderly. From 2011 to 2014 and in 2015–16, we conducted a multicentre test negative case control study in hospitals of 11 European countries to measure influenza vaccine effectiveness (IVE) against laboratory confirmed hospitalised influenza among people aged ≥65 years. We pooled four seasons data to measure IVE by past exposures to influenza vaccination.

We swabbed patients admitted for clinical conditions related to influenza with onset of severe acute respiratory infection ≤7 days before admission. Cases were patients RT-PCR positive for influenza virus and controls those negative for any influenza virus. We documented seasonal vaccination status for the current season and the two previous seasons.

We recruited 5295 patients over the four seasons, including 465A(H1N1)pdm09, 642A(H3N2), 278 B case-patients and 3910 controls. Among patients unvaccinated in both previous two seasons, current seasonal IVE (pooled across seasons) was 30% (95%CI: −35 to 64), 8% (95%CI: −94 to 56) and 33% (95%CI: −43 to 68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively. Among patients vaccinated in both previous seasons, current seasonal IVE (pooled across seasons) was −1% (95%CI: −80 to 43), 37% (95%CI: 7–57) and 43% (95%CI: 1–68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively.

Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred some protection to vaccinated patients against hospitalisation with influenza A(H3N2) and B. Vaccination of patients already vaccinated in both the past two seasons did not seem to be effective against A(H1N1)pdm09. To better understand the effect of repeated vaccination, engaging in large cohort studies documenting exposures to vaccine and natural infection is needed.

1. Background

The World Health Organization (WHO) strategy for seasonal influenza vaccination aims at reducing death and hospitalisation among individuals at risk of severe influenza [1]. In Europe, annual vaccination is recommended to individuals with specific underlying conditions and elderly [2]. Despite WHO recommendation to reach 75% coverage in elderly by 2010, uptake among Europeans aged 65 years and above was below 50% in 2014 [3]. Results of recent studies question the effect of repeated influenza vaccinations on influenza vaccine effectiveness (IVE) [4–7].

Immunologists suggest that past natural influenza infections may enhance immune response to new variant influenza viruses [8] and that genetic distances between consecutive vaccine components and circulating strains may affect IVE [6]. Previous seasons' vaccination may provide some residual protection but may also modify current seasonal IVE [4,5,9]. The few epidemiological studies describing the effect of repeated vaccinations, have mainly focused on primary care based studies with non-severe outcomes [4,5,9,10]. Further understanding the role of repeated vaccinations on seasonal IVE in elderly is important to better interpret current seasonal IVE, guide new vaccine development and, eventually, inform vaccination strategies [11].

We have set up two European networks of hospitals (InNHOVE 2011–14 & I-MOVE plus since 2015) allowing to measure seasonal IVE against laboratory confirmed hospitalised influenza among elderly [12–14]. The same generic protocol was used across seasons [15,16].

We pooled four seasons data to measure, among patients aged 65 years and above, the IVE against hospitalisations associated with influenza A(H3N2), A(H1N1)pdm09 and B infections according to past exposures to influenza vaccination.

2. Methods

We conducted a multicentre hospital-based case-control study using the test-negative design (TND) [17]. We included between three and twelve study sites per season in the analysis.

The study population consisted of all community-dwelling individuals aged 65 years and above admitted as inpatients with influenza related illness, and who had no contra-indication for influenza vaccination or previous laboratory confirmed influenza in the season.

We defined specific study periods for each influenza season, study site and influenza (sub)type as lasting from the week of the first to the week of the last laboratory confirmed case of a given (sub)type of influenza.

We included hospitalised patients who had in the past seven days at least one systemic (fever or feverishness, malaise, headache, myalgia) and at least one respiratory symptoms (cough, sore throat or shortness of breath).

In the participating services of each hospital, patients admitted for clinical conditions that could be related to influenza were screened for eligibility. The study teams swabbed patients meeting the inclusion criteria. Specimens were tested by RT-PCR and patients classified as influenza A(H1N1)pdm09, A(H3N2), B cases or controls if their specimens tested negative for all influenza viruses.

We documented seasonal vaccination status for the current season (defined as the season when the patients were included in the study and therefore tested positive or negative for influenza) and the two previous seasons. We defined patients as vaccinated if they had been vaccinated at least 14 days before symptoms onset. Otherwise, they were considered as unvaccinated.

Hospital study teams collected patients' demographic characteristics, date of current seasonal vaccination, underlying conditions (diabetes mellitus, obesity, cardiovascular, lung diseases, and cancer), number of hospitalisations for underlying diseases in the past 12 months and smoking status. Underlying conditions were collected through interviews with patients (or their relatives) and hospital and/or primary care databases. In Finland, Spain (including Valencia and Navarra) and Portugal, vaccination status was retrieved from vaccination registers. In study sites with no vaccination register, study teams collected vaccination status for current and past seasons through patients' interview. For patients vaccinated or unable to provide their vaccination status, study teams

Table 1
List of vaccine recommended components and predominant circulating strains in Europe (2011–14, 2015–16)[a]

Season	Vaccine strains			Main Circulating strain
	Penultimate season	Previous season	Current season	
Season 11–12	A/Brisbane/59/2007 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/Perth/16/2009(H3N2)-like
	A/Brisbane/10/2007 (H3N2)-like	A/Perth/16/2009(H3N2)-like	A/Perth/16/2009(H3N2)-like	
	B/Brisbane/60/2008-like (Victoria lineage)	B/Brisbane/60/2008-like (Victoria lineage)	B/Brisbane/60/2008-like (Victoria lineage)	
Season 12–13	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Perth/16/2009(H3N2)-like	A/Perth/16/2009(H3N2)-like	A/Victoria/361/2011(H3N2)-like MUTATION IN EGG_ADAPTED	A/Victoria/361/2011(H3N2)
	B/Brisbane/60/2008-like (Victoria)	B/Brisbane/60/2008-like (Victoria)	B/Wisconsin/61/2010-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)
Season 13–14	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Perth/16/2009(H3N2)-like	A/Victoria/361/2011(H3N2)-like MUTATION IN EGG_ADAPTED	A/Texas/50/2012(H3N2)-like	A/Texas/50/2012(H3N2)-like
	B/Brisbane/60/2008-like (Victoria lineage)	B/Wisconsin/61/2010-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)	
Season 15–16	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Texas/50/2012(H3N2)-like	A/Texas/50/2012(H3N2)-like	A/Switzerland/9715293/2013 (H3N2)-like	
	B/Massachusetts/2/2012-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)	B/Phuket/3073/2013-like (Yamagata)	B/Brisbane/60/2008-like (Victoria)

[a] Sources: http://www.who.int/influenza/vaccines/virus/recommendations/2016_17_north/en/; http://ecdc.europa.eu/en/publications/surveillance_reports/influenza/Pages/influenza_virus_characterisation.aspx.

called patients' GP or pharmacists or searched for vaccination passes to retrieve vaccination status and date of uptake.

For each season, we pooled data from participating hospitals. Using the odds ratio (OR) of being vaccinated between cases and controls we computed the VE as (1 – OR) x 100%. We performed a logistic regression to adjust IVE estimates for potential confounders. We used the one in ten rule of predictor degrees of freedom to events to determine the number covariates to include in analyses with low sample sizes in order to avoid overfitting the model [18,19]. We used a one-stage method with study site as a fixed effect. Due to low sample and inherent risks for overfitting, and based on previously published data [12–14], we apriori decided on adjustment variables. When sample size allowed, we further adjusted IVE estimates for month of symptoms onset, age (modelled as a restricted cubic spline with four knots) and presence of chronic conditions. We pooled data from seasons with circulation of the same (sub)type specific influenza and computed pooled IVE further adjusting on the season.

In a stratified analysis based on the data pooled across seasons and using unvaccinated in the current season as a reference, we compared VE measured in the current season between individuals who were vaccinated in the past season and those who were not vaccinated in the past season. Due to low sample size, we excluded patients vaccinated in only one of the two previous seasons from this analysis.

Using patients unvaccinated in current and the two previous seasons as the reference, we conducted an indicator analysis. We computed the effectiveness of being vaccinated in current season only, in previous season but not current (regardless of penultimate season vaccine status), and in current and both previous seasons for each season and overall. Due to low sample size, we excluded patients vaccinated in the penultimate season only, those vaccinated in the penultimate and current seasons only and those vaccinated in the previous and current seasons only.

We conducted sensitivity analyses restricted to patients for whom the vaccination status ascertainment was based on vaccination registers.

3. Results

We included 21 hospitals in 2011–12, 18 in 2012–13, 12 in 2013–14 and 25 in 2015–16. The 5295 patients recruited over the four seasons included 465A(H1N1)pdm09, 642A(H3N2), 278 B case-patients and 3910 controls (Table 2) for whom current vaccination status was available. Previous vaccination information was missing for 116 (8.2%) cases and 255 (6.5%) controls.

We included seasons 2012–13, 2013–14 and 2015–16 for A (H1N1)pdm09 analyses, seasons 2011–12, 2012–13 and 2013–14 for A(H3N2) and seasons 2012–13 and 2015–16 for influenza B analyses (Table 1).

3.1. Influenza A(H1N1)pdm09

Vaccine and circulating A(H1N1)pdm09 viruses remained stable across the study period (Table 1).

The median age was 76 years among A(H1N1)pdm09 cases and 79 years among controls ($p < 0.01$). A higher proportion of controls than cases had respiratory chronic conditions (47% vs 40%, $p < 0.01$) and were obese (21% vs 13%, $p < 0.01$). A higher proportion of A (H1N1)pdm09 cases than controls had cancer (25% vs 18%, $p < 0.01$) (Table 2).

Season specific IVE against A(H1N1)pdm09 virus ranged between 15% (95%CI: −51 to 52) in 2012–13 and 41% (95%CI: 20–57) in 2015–16. Pooled across 2012–13, 2013–14 and 2015–16, IVE against A(H1N1)pdm09 virus was 38% (95%CI: 21–51) (Table 3).

Table 2
Characteristics for influenza A(H1N1)pdm09, A(H3N2) and influenza B, and controls included in the study, InNHOVE 2011–14 and I-MOVE + 2015–16.

	A(H1N1)pdm09					A(H3N2)					B				
	Cases		Controls			Cases		Controls			Cases		Controls		
	(N = 465)	%	(N = 2462)	%	p-value	(N = 642)	%	(N = 1798)	%	p-value	(N = 278)	%	(N = 1996)	%	p-value
Median age	75.6		79.0		0.000	80.0		79.7		0.550	77.0		79.0		0.025
Sex = Male	0,557484	55.7	1353/2461	55.0	0.799	348/642	54.2	991/1798	55.1	0.712	136/278	48.9	1074/1995	53.8	0.140
Vaccine status															
Current season influenza vaccination	196/465	42.2	1493/2462	60.6	0.000	385/642	60.0	1186/1798	66.0	0.007	130/278	46.8	1216/1996	60.9	0.000
Previous two and current season vaccination															
None	200/423	47.3	669/2346	28.5	0.000	121/591	20.5	300/1671	18.0	0.332	95/255	37.3	556/1922	28.9	0.000
Current season only	15/423	3.5	95/2346	4.0		12/591	2.0	38/1671	2.3		9/255	3.5	78/1922	4.1	
Current and previous seasons	12/423	2.8	101/2346	4.3		36/591	6.1	92/1671	5.5		8/255	3.1	69/1922	3.6	
Current and penultimate seasons	8/423	1.9	80/2346	3.4		12/591	2.0	41/1671	2.5		1/255	0.4	63/1922	3.3	
All three seasons	153/423	36.2	1170/2346	49.9		321/591	54.3	1004/1671	60.1		111/255	43.5	970/1922	50.5	
Penultimate and previous seasons	18/423	4.3	135/2346	5.8		52/591	8.8	112/1671	6.7		20/255	7.8	110/1922	5.7	
Previous season only	8/423	1.9	32/2346	1.4		17/591	2.9	37/1671	2.2		2/255	0.8	28/1922	1.5	
Penultimate season only	9/423	2.1	64/2346	2.7		20/591	3.4	47/1671	2.8		9/255	3.5	48/1922	2.5	
Unknown vaccination status	*42*		*116*			*51*		*127*			*23*		*74*		
Presence of comorbidities															
Diabetes	135/455	29.7	759/2431	31.2	0.544	211/637	33.1	578/1786	32.4	0.730	75/257	29.2	595/1963	30.3	0.773
Cardiac disease	266/461	57.7	1422/2451	58.0	0.918	322/640	50.3	966/1795	53.8	0.128	148/275	53.8	1174/1987	59.1	0.103
Respiratory diseases	185/461	40.1	1152/2448	47.1	0.007	294/641	45.9	844/1795	47.0	0.645	104/276	37.7	971/1977	49.1	0.000
Cancer	114/460	24.8	437/2449	17.8	0.001	116/289	40.1	327/1071	30.5	0.002	30/273	11.0	362/1982	18.3	0.003
Obesity	59/458	12.9	511/2421	21.1	0.000	134/638	21.0	442/1783	24.8	0.058	49/272	18.0	401/1962	20.4	0.376
Any chronic disease	425/460	92.4	2279/2462	92.6	0.923	549/642	85.5	1605/1797	89.3	0.012	237/278	85.3	1861/1996	93.2	0.000
More than one chronic condition	313/457	68.5	1741/2451	71.0	0.288	370/642	57.6	1148/1798	63.8	0.006	158/276	57.2	1417/1988	71.3	0.000
Hospitalisations in previous 12 months	196/455	43.1	1044/2446	42.7	0.877	206/640	32.2	691/1797	38.5	0.005	89/276	32.2	857/1969	43.5	0.000
Current smoking	108/449	24.1	357/2386	15.0	0.000	81/640	12.7	193/1793	10.8	0.191	49/270	18.1	319/1910	16.7	0.544
Antivirals treatment prior to swabbing	42/463	9.1	45/2457	1.8	0.000	9/631	1.4	16/1782	0.9	0.452	19/275	6.9	36/1993	1.8	0.000
Delays symptoms onset – swabbing < 4 days	272/465	58.5	1298/2462	52.7	0.023	258/642	40.2	805/1798	44.8	0.046	127/278	45.7	1079/1996	54.1	0.010

Table 3
Adjusted vaccine effectiveness against influenza A(H1N1)pdm09, A(H3N2) and B by season, among patients aged 65 years and older, InNHOVE 2011–14 and I-MOVE + 2015–16.*

Influenza type/subtype	Season	Number of hospitals	N	Cases	Vaccinated cases	Controls	Vaccinated controls	IVE	95%CI
A(H1N1)pdm09	**Pooled**[a]		**2927**	**465**	**196**	**2462**	**1493**	**37.6**	**(20.6 to 50.9)**
	12–13[b]	18	1230	56	30	1174	755	15.1	(-51.2 to 52.3)
	13–14[c]	12	382	56	28	326	204	34.1	(-22.2 to 64.5)
	15–16[d]	25	1315	353	138	962	534	41.2	(20.3 to 56.7)
A(H3N2)	**Pooled**[e]		**2440**	**642**	**385**	**1798**	**1186**	**28.9**	**(13.2 to 41.7)**
	11–12[f]	21	1438	473	301	965	654	13.6	(-11.9 to 33.3)
	12–13[g]	18	417	44	17	373	252	62.5	(23.1 to 81.7)
	13–14[h]	12	585	125	67	460	280	40.3	(7.9 to 61.3)
B	**Pooled**[i]		**2274**	**278**	**130**	**1996**	**1216**	**44.3**	**(26.2 to 58.0)**
	12–13[j]	18	1165	172	81	993	636	38.0	(11.1 to 56.8)
	15–16[k]	25	1109	106	49	1003	580	50.5	(21.3 to 68.9)

List of study sites included in the analysis:
[a] ES FI FR HR IT LT NA NL PL PT RO VA.
[b] FR IT LT NA VA.
[c] FR NA.
[d] ES FI FR HR IT LT NA NL PL PT RO.
[e] FR IT LT NA VA.
[f] FR IT NA VA.
[g] FR IT LT NA VA.
[h] FR IT NA.
[i] ES FI FR HR HU IT LT NA NL PL PT RO VA.
[j] FR IT LT NA VA.
[k] ES FI FR HR HU IT LT NA NL PL PT RO.
* Adjusted for study site, date of onset, age, presence of at least one chronic condition and season.

Table 4
Influenza vaccine effectiveness for current season stratified by two previous seasons vaccination status by influenza (sub)type and season, InNHOVE, 2011–14 and I-MOVE + 2015–16.*

Type subtype	Seasons included	Among those not vaccinated in either of the two previous seasons				Among those vaccinated in both previous two seasons			
		Cases (vaccinated)	Controls (vaccinated)	VE	95%CI	Cases (vaccinated)	Controls (vaccinated)	VE	95%CI
A(H1N1)pdm09[1]	2012–13, 2013–14 and 2015–16	212 (14)	764 (95)	30	(−35 to 64)	171 (153)	1305 (1170)	−1	(−80 to 43)
A(H3N2)[2]	2011–12, 2012–13 and 2013–14	133 (12)	338 (38)	8	(−94 to 56)	373 (321)	1116 (1004)	37	(7 to 57)
B[3]	2012–13 and 2015–16	104 (9)	634 (78)	33	(−43 to 68)	131 (111)	1080 (970)	43	(1 to 68)

* Adjusted for study site, month of onset, age, presence of chronic conditions and season.
[1] Missing vaccination status for 42 influenza A(H1N1)pdm09 cases and 116 controls. Missing information on chronic conditions for 3 influenza A(H1N1)pdm09 cases.
[2] Missing vaccination status for 51 influenza A(H3N2) cases and 127 controls. Missing information on chronic conditions for 1 control.
[3] Missing vaccination status for 23 influenza B cases and 74 controls.

In the stratified analysis, current season IVE (pooled across seasons) was 30% (95%CI: −35 to 64) among those not vaccinated in either of the two previous seasons and −1% (95%CI: −80 to 43) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 39% (95%CI: 19–54). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was 30% (95%CI: −8 to 55) (Table 5).

3.2. Influenza A(H3N2)

Vaccine components, as recommended by WHO, were antigenically similar to circulating strains in all A(H3N2) seasons included in this analysis (table 1). In 2012–13, mutations in the egg-adapted A(H3N2) vaccine strain led to a vaccine strain antigenically distinct from the circulating one [20].

A(H3N2) case-patients had the same median age (80 years, p = 0.55) and sex ratio (p = 0.71) as their respective controls. A total of 85% of cases and 89% of controls had at least one underlying condition (p = 0.01) and 32% of cases and 38% of controls (p < 0.01) had been hospitalised for chronic conditions in the past 12 months (Table 2).

Season specific IVE against A(H3N2) virus ranged between 14% (95%CI: −12 to 33) in 2011–12 and 63% (95%CI: 23–82) in 2012–13. Pooled across 2011–12, 2012–13 and 2013–14, IVE against A (H3N2) virus was 29% (95%CI: 13–42) (Table 3).

In the stratified analysis, current season IVE (pooled across seasons) was 8% (95%CI: −94 to 56) among those not vaccinated in either of the two previous seasons and 37% (95%CI: 7–57) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 39% (95%CI: 19–53). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was 14% (95%CI: −23 to 40) overall. It was 25% (95%CI: −22 to 53) in 2011–12 and 9% (95%CI: −80 to 54) in 2013–14 (Table 5).

3.3. Influenza B

In 2012–13, vaccine and circulating lineages were Yamagata while vaccines contained Victoria in the two previous seasons. In 2015–16, the current and two previous seasonal vaccines contained a Yamagata component while the main circulating viruses were Victoria (Table 1).

Table 5
Previous, current and combined seasonal influenza vaccine effectiveness (VE) by influenza (sub)type and season, InNHOVE 2011–14 and I-MOVE + 2015-16.[†]

Season	Vaccine uptake in the current and past two seasons	Influenza A(H1N1)pdm09				Influenza A(H3N2)				Influenza B			
		Cases	Controls	IVE	95% CI	Cases	Controls	IVE	95% CI	Cases	Controls	IVE	95% CI
Season 11–12	None					68	96	Reference					
	Current only					6	10	21	(−162 to 76)				
	Previous season and not current					64	113	25	(−22 to 53)				
	All					255	559	37	(7 to 57)				
Season 12–13	None	18	291	Reference		15	82	Ref		52	257	Reference	
	Current only	4	57	−30[*]	(−304 to 58)	1	14	NA		4	44	43	(−72 to 81)
	Previous season and not current	6	121	23[*]	(−100 to 71)	5	31	NA		22	92	−31	(−137 to 28)
	All	24	591	34[*]	(−24 to 65)	14	207	NA		69	504	27	(−12 to 52)
Season 13–14	None	19	83	Reference		38	122	Reference					
	Current only	0	8	NA		5	14	−20	(−284 to 63)				
	Previous season and not current	8	36	12[*]	(−123 to 65)	20	52	9	(−80 to 54)				
	All	23	170	45[*]	(−8 to 72)	52	238	48	(12 to 69)				
Season 15–16	None	161	295	Reference						43	299	Reference	
	Current only	10	30	38	(−40 to 72)					5	34	−12	(−227 to 61)
	Previous season and not current	21	74	44	(−1 to 68)					9	94	23	(−76 to 66)
	All	106	409	45	(20 to 62)					42	466	50	(16 to 71)
Overall	None	198	669	Reference		121	300	Reference		95	556	Reference	
	Current only	14	95	30	(−33 to 63)	12	38	15	(−78 to 60)	9	78	29	(−49 to 67)
	Previous season and not current	35	231	30	(−8 to 55)	89	196	14	(−23 to 40)	31	186	−4	(−66 to 35)
	All	153	1170	39	(19 to 54)	321	1004	39	(19 to 53)	111	970	37	(12 to 54)

NA: not applicable (sample size too small to adjust IVE on study site).
[†] Adjusted for study site, month of onset, age, presence of chronic conditions and season unless otherwise specified.
[*] Adjusted for study site.

The median age was 77 years for Influenza B cases and 79 years for controls (p = 0.02). A higher proportion of controls than cases had respiratory chronic conditions (49% vs 38%, p < 0.01), cancer (18% vs 11%, p < 0.01) and were hospitalised for chronic conditions in the past twelve months (44% vs 32%, p < 0.01) (Table 2).

Season specific IVE against influenza B virus was 38% (95%CI: 11–57) in 2012–13 and 51% (95%CI: 21–69) in 2015–16. Pooled across 2012–13 and 2015–16, IVE against B virus was 44% (95% CI: 26–58) (table 3).

In the stratified analysis, current season IVE (pooled across seasons) was 33% (95%CI: −43 to 68) among those not vaccinated in either of the two previous seasons and 43% (95%CI: 1–68) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 37% (95%CI: 12–54). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was −4% (95%CI: −66 to 35) overall; −31% (95%CI: −137 to 28) in 2012–13 and 23% (95%CI: −76 to 66) in 2015–16 (Table 5).

In sensitivity analyses restricted to patients for whom vaccine status was ascertained using registries, point estimates were close to the original analysis point estimates in most instances. In the indicator analysis, point estimates sometimes derived from the original analysis but confidence intervals in both analyses largely overlapped (Supplementary Tables 1 and 2).

4. Discussion

Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred protection to vaccinated patients against hospitalisation associated with influenza infections in all instances except against A(H1N1)pdm09 among patients vaccinated in both the previous two seasons. Taking as a reference patients unvaccinated in the past two and the current season, the highest IVE point estimate was systematically observed among patients vaccinated in all three (current and two previous) seasons.

As in previously published studies [5,9,13], we used patients never vaccinated in three seasons as reference to measure the effect conferred by various vaccination patterns in the three seasons. This also allowed us to discuss the residual effect of previous vaccination, alone or combined with vaccination in the current season. Using a stratified analysis with patients unvaccinated in the current season as reference, we measured how much former vaccination modified the effectiveness of current vaccination. This allowed us to discuss the protection conferred by the current season vaccine, provided recent vaccine history.

Limitations need to be discussed before further interpreting our results.

High risk groups may be more likely to be vaccinated and to develop a severe form of influenza, leading to chances for underestimation of IVE. In our study, adjustment on underlying chronic conditions or hospitalisation for chronic conditions in the previous year did not change the IVE estimates. However, unmeasured confounding cannot be excluded. Previous seasons' vaccination status was missing for less than 10% of patients. Vaccination status ascertainment relied on patients' and physicians' interviews for 32% of recruited patients; otherwise vaccination status was ascertained based on vaccine registries. Recall bias on vaccination status (previous and current vaccinations) could affect IVE estimates if differential between cases and controls. We believe that differential recall bias is not present in our study as vaccination status was collected independently from the patients' laboratory results. Furthermore, the results were similar when restricting to patients with vaccination status extracted from vaccination registers.

The literature suggests that elderly have consistent vaccination habits over time. Having been vaccinated in the past seasons was reported as a strong predictor of current vaccination status [21–23]. This led, in our study, to small number of patients with changing vaccination status. Despite pooling seasons we still had low precision estimates of current IVE according to past seasons vaccination. We cannot exclude that the observed differences are due to random errors. Due to small sample size, we could not interpret season specific results. The role of previous vaccination on current IVE may vary by season as genetic distance between previous and current vaccine strains as well as with the circulating strains change. Prior vaccination may negatively interfere with current vaccine when antigenic distance between vaccine and circulating strains is large but distance between consecutive vaccine components is small [6]. Enlarging the number of participating hospitals will allow measuring seasonal effect of previous vaccination on current IVE with more precise estimates.

Our study population was elderly population in the EU. They are offered annual vaccination for free [24] and have a higher probability than younger adults of having been exposed to influenza viruses in the past. Effects of previous vaccination and/or infection on IVE may be of different magnitude according to birth cohorts. Epidemiological inputs into these theories would require setting up longitudinal studies with prospective collection of vaccination status and natural infection.

Keeping in mind the above limitations, our results suggest some residual effects from previous year vaccination against A(H1N1) pdm09 virus, a very limited effect against A(H3N2) virus and no effect against influenza B virus. Residual protection against A (H1N1)pdm09 virus was previously suggested [25] and may be explained by some antigenic stability of A(H1N1)pdm09 viruses over time [26]. These results are also consistent with findings suggesting stable within-season IVE against A(H1N1)pdm09 [27] and decreasing IVE against A(H3N2) and B viruses. On the other hand, recent findings from McLean et al. measuring IVE against primary health care endpoints among adults suggested some residual protections against influenza A(H3N2) and B viruses [9]. Diminished immune response to influenza vaccination in elderly compared with younger age group [28] could lead to shorter duration of protection among older adults and explain the discrepancy between McLean's and our results. The small number of seasons included in this analysis may also explain differences observed with McLean et al. We included only two influenza B seasons with different patterns in terms of consecutive circulating and vaccine lineages and we could rely only on surveillance data to interpret lineages circulation. Lineage characterisation at the individual level would ease the interpretation of our results. Understanding previous effect of seasonal vaccination against influenza B may help vaccine lineage selection. Among possible lineage selection strategies, the yearly alternative approach proposes to alternate one Yamagata and one Victoria strain, assuming a one-year residual protection against the other lineage [31].

Stratified analyses suggested some interference from previous vaccinations on current season IVE against A(H1N1)pdm09 (negative effect) and against A(H3N2) (positive effect) but very limited effect against influenza B viruses. We observed that current season IVE against A(H1N1)pdm09 viruses was close to null among patients vaccinated in both previous two seasons and 30% among patients not vaccinated in either of the two previous seasons. This observation, potentially explained by residual protection from previous vaccination, is in line with a recently published study concluding that current influenza vaccination or several prior doses are needed to have a high protective effect against A(H1N1) pdm09 viruses [32]. Despite largely overlapping confidence intervals, our stratified analysis suggested that patients previously vaccinated had a higher current seasonal IVE (37% when vaccinated in both previous seasons) against A(H3N2) viruses compared with patients unvaccinated in the previous seasons (8%). Although antibody titers are poor surrogates for vaccine protection [33], such positive effect has been previously suggested for A(H3N2) viruses based on comparison of sero-responses to different vaccination patterns [34]. Most studies measuring VE against medically-attended influenza A(H3N2) in adults reported negative effect of repeated vaccination against A(H3N2) viruses. Authors of these studies hypothesised that this negative effect could be due to either the original antigenic sin [9,35] or antigenic distance hypothesis [5]. None of the A(H3N2) seasons included in our analysis met the criteria to fulfill the antigenic distance hypothesis. Furthermore, these differences between our results and published studies may reflect random errors due to small numbers or differences in the outcomes and study populations.

5. Conclusion

To our knowledge, this work is the largest hospital based IVE study presenting the effects of repeated vaccination. Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred protection to vaccinated patients against hospitalised influenza in all instances except against A (H1N1)pdm09 viruses among patients vaccinated in the past two seasons. Meanwhile, working on a different, long lasting and more efficient influenza vaccine is urgent. Engaging in longitudinal studies, prospectively collecting exposure to both influenza vaccination and influenza infection, is needed to understand potential interferences between consecutive vaccinations. Acquiring such knowledge is crucial at a time when universal influenza vaccination is being recommended in an increasing number of countries.

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Potential conflicts of interest

GlaxoSmithKline, Sanofi Pasteur and Sanofi Pasteur MSD financially supported the InNHOVE network. They had no role in study design, data collection, pooled analysis, and publication. JPB reports grants and study support from Foundation for Influenza Epidemiology and Sanofipasteur, and personal fees from Novavax and Seqirus. In Finland, THL has a policy of public-private partnership. Ritva Syrjänen is a co-investigator in pneumococcal studies (not related to this study) for which THL has received research support from GlaxoSmithKline Biologicals. All other coauthors have no conflicts of interest to declare.

Authors' contribution

Marc Rondy was involved in the original methodological design of the study (generic protocol). He coordinated the European hospital IVE network, undertook the statistical analysis on which the research article is based and led the writing of the research article. Alain Moren initiated the original methodological design of the study. He coordinated the European hospital IVE network and contributed to the writing of the research article.

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The InNHOVE/I-MOVE + working group contributors contributed to developing the study site specific protocol. They were in charge of supervising the study at the hospital level and collect the data published in this research article. They read, contributed and approved the manuscript final version.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.06.088.

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